abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Office Action. Applicants reserve the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional applications.

Rejections under 35 U.S.C. §112

Claims 8 and 24 are rejected under 35 U.S.C. §112, first paragraph, "because the specification, while being enabling for a method of treatment using chimeric antibodies wherein the antibodies are anti-VEGF murine antibodies which have human heavy and light constant chain domains in place of the homologous murine sequences, does not reasonably provide enablement for a method of treatment using chimeric antibodies."

In the interest of expediting the prosecution process, claim 24 has been canceled and claim 8 amended. The amended claim 8 encompasses a chimeric murine antibody wherein at least one constant chain domain is replaced by the homologous human sequence. The specification provides enabling disclosure for the claimed subject matter as amended. With regard to "the production of other types of fusion proteins" which, according to the Examiner, would fall into the category of "chimeric" antibody (Office Action, page 5, lines 2-3), Applicants point out that the specification provides ample guidance for variant antibodies, including but not limited to, conjugates with cytotoxic moieties (pages 14-15); fusions with non-immunoglobulin polypeptides (pages 15-16); and heterospecific antibodies capable of binding hVEGF and a non-hVEGF epitope (page 16-17). All these variant antibodies can be readily made by, for example, recombinant methods that were well known in the art. Applicants expressly reserve the right to pursue such variant antibodies during the pendency of this application.

In view of the claim amendments, Applicants respectfully request removal of the rejection under 35 U.S.C. §112, first paragraph.

Claims 8 and 24 are also rejected under 35 U.S.C. §112, second paragraph as allegedly being indefinite for the use of the term "chimeric." Again, claim 24 has been canceled and claim 8 has been amended to more clearly define the claimed subject matter as a chimeric murine antibody wherein at least one constant chain domain is replaced by the homologous human sequence.

Claims 1, 2 and 22 are rejected under 35 U.S.C. §112, second paragraph for not containing a positive process step which clearly relates back to the preamble. Claims 2 and 22 have been canceled. Claim 1 has been amended to include a step to determine the reduction of cerebral edema upon administration of anti-VEGF antibody. Applicants submit that the amendments are responsive to the Office Action and the amended claims are in compliance with the requirement under 35 U.S.C. §112, second paragraph. The rejections are therefore respectfully requested to be withdrawn.

Rejection under 35 U.S.C. §102 (b)

Claims 1 and 8-10 are rejected under 35 U.S.C. §102 (b) as being allegedly anticipated by WO94/10202 as evidenced by Taber's Cyclopedic Medical Dictionary and the Risau reference. According to the Examiner, WO94/10202 teaches a method of treating a tumor with hVEGF antagonist and specifically teaches treating glioblastoma and edema associated with brain tumors.

Applicants submit that claim 1 has been amended to encompass a method of treating a mammal having cerebral edema, comprising administering effective amount of anti-hVEGF antibody, and determining the degree of cerebral edema, whereby anti-hVEGF antibody reduces cerebral edema. Thus, the claim as amended is directed specifically to reducing cerebral edema. The formation of cerebral edema is a major complication associated with a number of CNS pathological conditions. Prior to the present invention, the direct role of VEGF in the formation of cerebral edema was unclear with contradictory experimental observations reported in the literature. For example, as cited in the background section of the present specification (page 4, lines 8-17), Nag et al., *J. Neuropathology and Experimental Neurology* 56:912 (1997), in their cortical cold-injury rat model, demonstrated the presence of mural VEGF in permeable pial vessels and arterioles within the damaged tissue and, from this observation, it was inferred that VEGF is one of several factors that may mediate BBB breakdown and edema formation. On the other hand, in Hayashi et al., *J. Cerebral Blood Flow and Metabolism*, 18:887 (1998), it is reported that VEGF itself, when applied topically on the surface of a reperfused rat brain after transient cerebral artery occlusion, reduced ischemic brain damage, infarct volume and edema formation. The work done by the inventors of the present invention and described in the present application provides, for the first time, direct *in vivo* evidence that VEGF is responsible for the

cortical edema formation and that VEGF antagonist is effective to reduce the edema formation (see, for example, Example 7 of the specification).

Thus, in view of the amendment made in claim 1 and for the reasons set forth above, Applicants submit that the rejection under 35 U.S.C. §102 (b) has been overcome and respectfully request its withdrawal.

Rejection under 35 U.S.C. §103

Claims 1, 2, 8-10, 22 and 24-26 are rejected under 35 U.S.C. §103 as allegedly being unpatentable over WO94/10202 as evidenced by Taber's Cyclopedic Medical Dictionary and Risau in view of US Patent Nos. 5,955,311 and 5,306,710. The subject claims are also rejected under 35 U.S.C. §103 as allegedly being unpatentable over US Patent No. 5,955,311 in view of US Patent No. 5,306,710 and WO94/10202 as evidenced by Taber's Cyclopedic Medical Dictionary and Risau. Applicants respectfully traverse these rejections. Claims 2, 22 and 24-26 have been canceled, and the subject matter of claim 2 has been incorporated into the amended claim 1.

As discussed above in response to the rejection under 35 U.S.C. §102 (b), claim 1 as amended is directed specifically to reducing cerebral edema, which is a major complication associated with a number of CNS pathological conditions. Although VEGF has been known to be involved in many biological and pathological processes, and VEGF antagonists such as anti-VEGF antibodies have been shown to inhibit growth of tumors such as glioblastoma, the direct role of VEGF in cerebral edema formation had been unclear prior to the present invention. Contradictory experimental observations had been cited in the literature. Using a VEGF antagonist to sequester VEGF, the present invention for the first time demonstrated that VEGF is responsible for the cortical edema formation, and that VEGF antagonist such as anti-VEGF antibody is effective in reducing the edema formation.

Thus, Applicants submit that none of the cited references or combinations thereof teach reduction of cerebral edema formation by administering effective amount of anti-VEGF antibody. In light of the uncertainty in the field regarding the VEGF's direct role in cerebral edema formation, one of ordinary skill in the art at the time of invention would not have been motivated to practice the claimed invention with reasonable expectation of success. Applicants respectfully request that the rejections under 35 U.S.C. §103 be reconsidered and withdrawn.

In view of the amendments made, and for the reasons set forth hereinabove, Applicants submit that the claims are now in condition for allowance. An early Notice to that effect is respectfully requested. In the event that the Examiner wishes to discuss any aspect of this response or of the application, she is invited to telephone the undersigned attorney at (650) 225-8674. Applicants will be pleased to submit documents necessary to advance this application to issuance.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicants petition for any required relief including extension of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 07-0630. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,
GENENTECH, INC.

Date: December 5, 2000

By: Steven X. Cui
Steven X. Cui
Reg. No. 44,637
Telephone: (650) 225-8674

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